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EXAMINER	
ROBINSON, HOPE A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Application Status

1. Applicant's response filed to the Office Action mailed on November 17, 2008 on April 10, 2009 is acknowledged. The Notice of Appeal filed on November 4, 2009 is acknowledged.

Claim Disposition

2. Claims 79-84 and 91-99 are pending and are under examination.

Maintained-Claim Objection

3. Claims 79-81 are objected to because of the following informalities:

For clarity it is suggested that claim 79 is amended to read "...by a set of amino acid substitutions selected from the group [of sets] consisting". See the acceptor and donor language in the claim. See also claims 80-81.

Correction is required.

Maintained-Claim Rejections - 35 USC ∋ 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 79-81, 91-93, 97 and 99 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a donor fluorescent protein moiety and an acceptor fluorescent moiety contained in SEQ ID NO:2 with specific mutations to SEQ ID NO:2 at the positions listed in for example claim 79 and the disclosure in U.S. Patent No. 5,981,200, (for example, wherein the linker is a peptide moiety that does not emit light to excite the donor fluorescent protein moiety), does not reasonably provide enablement for mutations to the donor and acceptor moieties that are "85% identical to SEQ ID NO:2" that may not produce FRET or similar variability in the linker moiety. In addition, the claims read on any linker and the specification is not enabled for any linker as the linker moiety may refer to a single amino acid or a group or any linker with a protease recognition site for any protease. While the specification is enabled for linkers that are not fluorescent, is not enabled for linkers that are fluorescent. Further, the specification while enabled for linkers about 5-50 amino acids (see page 2 of the specification) is not enabled for linkers with the lengths encompassed in the breath of the claims. This means that amino acids can be added to the C or N terminus and the greater the length of the linker the less proximity the donor and acceptor moieties will have to each other and this will affect the energy transfer. It the moieties are far apart then the interaction will not be great or even exist.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include, but are

not limited to: quantity of experimentation necessary; amount of direction or guidance presented; presence or absence of working examples; nature of the invention; state of the prior art relative skill of those in the art; predictability or unpredictability of the art and breadth of the claims, each of which will be discussed below.

The claims are directed to a tandem fluorescent protein construct, comprising a donor fluorescent protein moiety, an acceptor fluorescent protein moiety and a linker moiety that couples the donor and acceptor moieties and wherein the donor and acceptor moieties exhibit FRET when the donor moiety is excited by radiation, characterized in that the linker moiety comprises a protease cleavage recognition site, wherein cleavage of the linker by a protease results in a change in FRET between the donor and acceptor moieties. The specification on page 8, line 12-15 appears to describe linkers as encompassing in scope those molecules that can be fluorescent in the same manner as the donor and acceptor moieties (in defining the "linker moiety" as a "radical" in the same manner as the fluorescent protein moieties). The specification only provides guidance for the use of linkers as a non-fluorescent moiety that provides at least the appropriate degree of separation between donor and acceptor moieties. There is no guidance to use the linker in any other manner, and the effect of having an additional fluorescent moiety between the donor and acceptor would have unpredictable consequences on resonance transfer, which as taught on page 12 of the instant specification is extremely sensitive to the degree of separation between donor and acceptor. One of skill in the art would have to engage in undue experimentation to provide linkers with the properties encompassed by the claims given these factors. The claims are also directed to donor and acceptor moieties comprising SEQ ID NO:2 comprising several amino acid substitutions. Therefore the claims encompass undefined

structures or multiple fluorescent moieties for which the specification is not enabled. To construct and test the many protein fragments encompassed in the claim to see the desired properties are retained would require undue experimentation.

Additionally, the specification fails to describe or provide any identifying characteristics or properties for the "other mutations" encompassed in the open claim language or provide data to demonstrate that function is retained or that the protein moieties exhibit FRET. Therefore, while it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. For example, Heim et al. (PNAS, vol. 91, pages 12501-04, 1994) disclose that a mutated DNA was sequenced and found to contain five amino acid substitutions, only one of which was found to be critical, Tyr66His, in the center of the chromophore. Heim et al. also disclose further site directed mutagenesis and noted that there was tolerance of the substitutions made, however, some mutants were weakly fluorescent (page 12504). The substitutions contemplated by the instant invention is greater than that proposed in the art, hence the specification should provide guidance as to what portion of the sequence is conserved and define the "other mutations" encompassed in the "comprising" language.

In addition, the specification on page 20, line 31 discloses that the optimal distance between the donor and acceptor sites is between about 1nm to about 10nm for the claimed resonance energy transfer to be useful. However, the "fluorescent protein moieties" encompass fluorescent peptide fragments of the intact fluorescent proteins, the distance between donor and acceptor may be about as short as the length of the linker. On page 20 of the specification it is

stated that the length of the linker moiety is chosen to optimize both FRET and the kinetics and specificity of enzymatic cleavage. Thus, if the linker is too short, the protein moieties may sterically interfere with each other's folding or with the ability of the cleavage enzyme to attack the linker. However, the claims broadly encompass linkers that are greater than 5-50 amino acids or 1-10nm in length which is not supported by the instant specification that discloses that linker length is a critical parameter required for the tandem conjugates to work and that linker lengths beyond about 1-10nm would unpredictably result in interference with polypeptide folding, enzyme cleavage, insufficient resonance transfer, or linker cleavage specificity. Moreover, the claims recite two fluorescent protein moieties said to be linked to one another via a linker moiety, the specification does not provide guidance as to covalent binding occurring via cyclization and oxidation of amino acids of the donor and acceptor protein moieties, or via any other methods considered to produce the "coupling" of the donor and acceptor protein moieties. No information is provided as to how the individual fluorescent moieties are to be isolated and ultimately linked to one another via any linking moiety. Thus, absent adequate guidance/direction regarding for example, the linker length, based on the breath of the claims, the undefined structures encompassed by the claims, the nature of the invention and the unpredictability of the linker as recited in the claims, a skilled artisan would not be able to practice the claimed invention commensurate in scope with the claims.

In view of the foregoing, one of skill in the art would require guidance, beyond that provided in the instant specification, in order to make the claimed tandem fluorescent protein in a manner that reasonably correlated with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

Maintained- Basis For Non-Statutory Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 79-84 and 91-99 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 and 43-44 of U.S. Patent No. 6,803,188. Although the conflicting claims are not identical, they are not patentably distinct

from each other because the claims in each are directed to tandem fluorescent protein constructs comprising a donor fluorescent moiety, an acceptor fluorescent moiety linked by a linker moiety, wherein the donor and acceptor moieties exhibit fluorescence resonance energy transfer (FRET) when said donor is excited and wherein the linker moiety has a protease cleavage recognition site. Both sets of claims recite substitutions that can occur to the donor and acceptor moieties which comprise an *Aequorea* fluorescent protein with respect to SEQ ID NO:2. Note that the modifications contemplated in the patent are encompassed in the instant application and therefore the limitations in the instant application are considered obvious in light of the patented claims; the claims of the patent are generic to the instant claims. Therefore, the claims of the patent and the instant application claims are an obvious variation of each other.

Response to Arguments

7. The response filed has been considered. The rejections of record remain under 35 USC 112, first paragraph and Obvious-Type Double Patenting as no amendments were made in attempts to obviate the rejections of record and no Terminal Disclaimer was filed.

Conclusion

8. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652